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Temporal effects of antibiotic use and hand rub consumption on the incidence of MRSA and *Clostridium difficile*

Nathalie Vernaz[1], Hugo Sax[2], Didier Pittet[2], Pascal Bonnabry[1], Jacques Schrenzel[3] and Stephan Harbarth[2]*

[1]Pharmacy Department, University of Geneva Hospitals and Medical School, Geneva, Switzerland; [2]Infection Control Program, University of Geneva Hospitals and Medical School, Geneva, Switzerland; [3]Clinical Microbiology Laboratory, University of Geneva Hospitals and Medical School, Geneva, Switzerland

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***Objectives*: The aim of this study was to determine the temporal relation between the use of antibiotics and alcohol-based hand rubs (ABHRs) and the incidence of methicillin-resistant *Staphylococcus aureus* (MRSA) and *Clostridium difficile*.**

***Methods*: An interventional time-series analysis was performed to evaluate the impact of two promotion campaigns on the consumption of ABHRs and to assess their effect on the incidence of non-duplicate clinical isolates of MRSA and *C. difficile* from February 2000 through September 2006. This analysis was combined with a transfer function model of aggregated data on antibiotic use.**

***Results*: Consumption of ABHRs correlated with MRSA, but not with *C. difficile*. The final model demonstrated the immediate effect of the second hand hygiene promotion campaign and an additional temporal effect of fluoroquinolone (time lag, 1 month; i.e. antibiotic effect delayed for 1 month), macrolide (lag 1 and 4 months), broad-spectrum cephalosporins (lag 3, 4 and 5 months) and piperacillin/tazobactam (lag 3 months) use. The final model explained 57% of the MRSA variance over time. In contrast, the model for *C. difficile* showed only an effect for broad-spectrum cephalosporins (lag 1 month).**

***Conclusions*: We observed an aggregate-level relation between the monthly MRSA incidence and the use of different antibiotic classes and increased consumption of ABHR after a successful hand hygiene campaign, while no association with ABHR use was detected for *C. difficile*.**

Keywords: cross-infection, prevention and control, alcohol, hand hygiene, methicillin resistance, *Staphylococcus aureus*, colitis, intervention model, transfer function model, health policy making

Introduction

Although the role of antibiotics in the epidemiology of methicillin-resistant *Staphylococcus aureus* (MRSA) and *Clostridium difficile* has been extensively studied, many controversies persist.[1,2] In particular, it remains unclear to what extent antibiotic stewardship may decrease MRSA or *C. difficile* acquisition within hospitals.

Previous studies have suggested that time-series analysis may be an accurate tool to describe the association between in-hospital antibiotic consumption and the incidence of antibiotic-resistant pathogens, including *C. difficile*.[3] Only a few, however, included the effect of the time-varying use of alcohol-based hand rubs (ABHRs), which may have an important effect on cross-transmission.[4–8] This is particularly important, since some experts have suggested that the promotion of ABHR may increase the spread of *C. difficile* due to their lack of sporicidal activity.[9,10]

At the University of Geneva Hospitals (HUG), MRSA has reached endemic levels. Despite the positive impact of a hospitalwide campaign promoting the use of bedside hand antisepsis on the prevalence of MRSA between 1994 and 1997,[4,11] we have observed an increase in the number of patients colonized and/or infected by MRSA since 1998. In response to this worrisome trend, two campaigns were launched to reinforce compliance with standard precautions and hand hygiene.

Hitherto, we have assessed neither the dynamic effect of these campaigns nor the influence of antibiotic selection

*Corresponding author. Tel: +41-22-372-3357; Fax: +41-22-372-3987; E-mail: stephan.harbarth@hcuge.ch

pressure on the local epidemiology of MRSA and *C. difficile*. In this paper, we attempted to determine the temporal association between antibiotic use, the use of ABHRs and the occurrence of MRSA and *C. difficile* at our institution. In particular, we assessed whether the isolation of MRSA and *C. difficile* was temporarily associated with the in-hospital use of several classes of antimicrobial agents.

Methods

Setting

The HUG are a 2200 bed primary and tertiary healthcare centre, including 37 adult intensive care unit beds, 923 acute care beds, 761 rehabilitation, geriatric and long-term care beds, 129 paediatric beds and 348 psychiatric beds, with ~45 000 admissions and over 850 000 outpatient visits each year.

Interventions

Antibiotic usage. During the study period, there was no institutional policy regarding the antibiotic use at HUG. Education and other methods to improve the antimicrobial use have not been implemented on a systematic basis. The therapeutics committee provides some recommendations regarding costly antibiotics. However, restriction is rare. Moreover, at the pharmacy level, refusal to dispense a drug is uncommon and physicians can prescribe any antimicrobial agent available at HUG.

Hand hygiene. Since 1994, an ABHR formula (Hopirub®) for hand antisepsis produced locally by the hospital pharmacy has been widely available to staff in the form of pocket-sized bottles and has been used throughout the hospital as the agent of choice for hand hygiene.[12,13] In spring 2003, a programme applying social marketing theory was initiated for the homogeneous implementation of standard precautions and isolation precautions under the registered trademark of '*VigiGerme*®'.[13] Although *VigiGerme*® mentioned hand hygiene as an element of standard precautions, it did not target the promotion of ABHR in particular. As part of a Swiss national hand hygiene promotion campaign and the Global Patient Safety Challenge entitled '*Clean care is safer care*', and organized by the World Health Organization (WHO),[14] the second initiative started in autumn 2005 with an exclusive focus on the frequent and proper use of ABHR.

MRSA and C. difficile control policy. The institutional strategy to control MRSA is based on different components that have been described previously.[11,15,16] In brief, these include systematic on-admission screening and pre-emptive isolation in the critical care setting, isolation in single rooms, when available, screening of roommates as soon as a new MRSA carrier has been identified, a computerized laboratory alert system[17] and topical decolonization of known MRSA carriers without risk factors for persistent carriage.[18]

Hospital policy to prevent the spread of *C. difficile* comprises several evidence-based elements[19]: contact isolation, thorough environmental cleaning with bleach and adequate antibiotic treatment. For sporadic cases, the use of ABHR after glove removal is not discouraged. Figure 1 summarizes the details of the study population, definitions and infection control policies implemented during the study period, as proposed by the ORION statement.[20]

Data collection

Monthly aggregated data of all antimicrobial drugs delivered to the entire institution were provided by the pharmacy department from February 2000 to September 2006. Paediatrics and psychiatry were excluded. Following the WHO's recommended metric, the defined daily dose (DDD), i.e. the assumed average maintenance dose per day for a drug used for its main indication in an adult, antibiotic usage was expressed as monthly aggregated DDD and normalized per 100 patient-days (antibiotic use density).[21] Monthly use of litres of ABHR were also collected and normalized per 100 patient-days,

<table>
<tr><td>Setting: 2200 bed primary and tertiary care teaching hospital in Switzerland. Paediatrics and psychiatry were excluded from this analysis. Infection control programme with one director, three associate hospital epidemiologists and nine full-time infection control nurses.</td><td>Dates:
February 2000 to September 2006.</td><td>Population characteristic: Mean hospitalization days, 51 524 per month (range, 48 102–55 128). Endemic MRSA, with clone ST228 representing the predominating strain since 1999. Sporadic Clostridium difficile with occasional small clusters.</td></tr>
<tr><td colspan="3">Infection control campaigns during the study: HUG launched two hospitalwide promotion campaigns; VigiGerme® in spring 2003 and 'Clean care is safer care' in autumn 2005 (including hand hygiene observations of healthcare personnel).</td></tr>
<tr><td colspan="3">Antibiotic use: During the study period, there was no institutional antibiotic policy; physicians could prescribe any antimicrobial agent available at HUG. Beginning in March 2006, HUG experienced a shortage of cefepime leading to an increase in piperacillin/tazobactam use.</td></tr>
<tr><td colspan="3">MRSA control policy: Systematic pre-emptive isolation in the critical care setting; contact isolation of MRSA carriers in single rooms, when available; use of dedicated material (e.g. gown, gloves, mask if indicated); computerized laboratory alert system; topical decolonization (nasal mupirocin ointment and chlorhexidine body washing) of known MRSA carriers without risk factors for persistent carriage.[18]</td></tr>
<tr><td colspan="3">MRSA screening policy: Systematic on-admission screening in the critical care setting; screening of room-mates as soon as a new MRSA carrier has been identified; universal MRSA on-admission screening from January to August 2003 in the entire hospital[28] and from October 2004 to May 2006 in selected surgical wards.[16] Screening sites: nose, groin, skin lesions, infected sites.</td></tr>
<tr><td colspan="3">C. difficile control policy: Contact isolation, thorough environmental cleaning with bleach and adequate antibiotic treatment.</td></tr>
<tr><td colspan="3">Definition of MRSA and C. difficile incidence: Number of clinical isolates per 100 patient-days, eliminating duplicates and surveillance swabs.</td></tr>
</table>

Figure 1. Population, setting, dates, definitions, antibiotic policy, promotion campaigns and infection control interventions. MRSA, methicillin-resistant *S. aureus*; HUG, Geneva University Hospitals; ST, sequence type.

as well as the hospital occupation rate expressed as occupied beds per 100 patient-days.

Monthly aggregated data on the number of new clinical MRSA isolates (excluding surveillance swabs and duplicates) were collected and expressed as an incidence density, i.e. the number of MRSA cultures per 100 patient-days.[11] For *C. difficile* occurrence, we used equivalent monthly incidence data based on laboratory-based surveillance.

Statistical analysis

Since temporally sequenced observations on MRSA and *C. difficile* are not independent, applying simple regression analysis would be inappropriate to evaluate these data.[22] Therefore, time-series analysis was used to examine the trends and autocorrelations over time, including characteristics for each explanatory variable and the outcomes of interest (MRSA and *C. difficile* incidence). We chose autoregressive integrated moving average (ARIMA) models using the Box–Jenkins method for analysis, which allow the stochastic dependence of consecutive data to be modelled.[23] Moreover, the methodology developed by López-Lozano and Monnet was applied to our data.[3,24,25]

We built an intervention model to determine if the two promotion campaigns significantly changed ABHR consumption. In an intervention model, the time series is constituted by an indicator variable containing discrete values. It may change due to an intervention interrupting the stationary evolution of the series, which, in the absence of the intervention, is usually assumed to be a pure ARIMA process.[23] To evaluate the effect of the two campaigns, we created dummy variables, with 0 and 1 representing pre-intervention and post-intervention periods, respectively.

Using two transfer function models, we assessed the association between the 'response' time series of the monthly incidence density of MRSA and *C. difficile* in terms of non-duplicate clinical isolates per 100 patient-days and the 'explanatory' time series of antibiotic usage, bed occupation rate and ABHR use (intervention model), taking into account the possible time delays of the effects (antibiotic and ABHR use) of up to 5 months.

A transfer function model consists of modelling a time series as a function of its past values and random errors. For each individual series, we identified and fitted an ARIMA model according to Box and Jenkins and therefore performed the following steps.[23] We first checked if the series were stationary (i.e. having a constant mean and variance), then identified the model by determining the ARIMA model orders (p,d,q) with the autocorrelation and partial autocorrelation, then estimated the model parameters by unconditional least squares method and finally checked the adequacy of the model and statistical significance of the parameters. Among different models, we chose the most parsimonious one with the fewest parameters. The generated coefficient (R^2) measures the overall fit of the regression line, expressing how close the points are to the estimated regression line in the scatter plot. In other terms, R^2 is the fraction of the variance of the dependent variable explained by the regression model.

After identification of the transfer function models, we determined the cross-correlation function estimating the correlations between the antibiotic use series at different time lags, the ABHR intervention model, occupation rate and the MRSA and *C. difficile* series. Significance tests for parameter estimates were used to eliminate the unnecessary terms in the model. A P value of <0.05 was considered to be statistically significant. All statistical analyses were performed with EViews 3 software (QMS, Irvine, CA, USA).

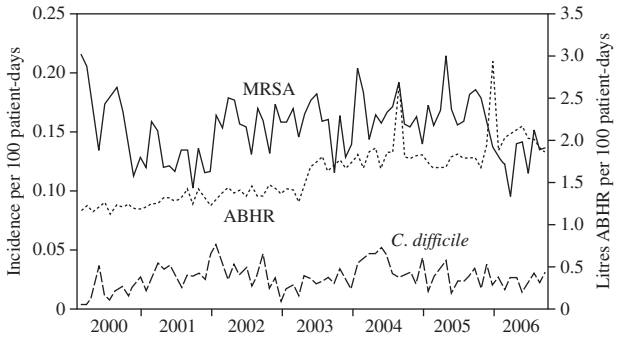

Figure 2. Monthly incidence of non-duplicate clinical isolates of *C. difficile* and MRSA, per 100 patient-days on the left-hand scale and litres of ABHRs per 100 patient-days on the right-hand scale. University of Geneva Hospitals, February 2000 to September 2006. The two peaks of ABHR use in 2004 and 2006 represent artificial increases due to the massive, single-time over-ordering of ABHRs by the adult intensive care units.

Results

Incidence of MRSA and C. difficile

Figure 2 shows the monthly incidence of non-duplicate MRSA and *C. difficile* clinical isolates per 100 patient-days. The average monthly MRSA incidence was 0.15 clinical isolates per 100 patient-days, varying from 0.09 to 0.21. No overall trend was observed throughout the period ($P = 0.71$). We identified an ARIMA model with one significant autoregressive term of order (lag) 1 month ($R^2 = 0.25$).

During the same period, the monthly incidence of *C. difficile* was 0.027 isolates per 100 patient-days, varying from 0.004 to 0.054, without any trend ($P = 0.82$). From these monthly data, we built a second ARIMA model, which showed an autoregressive term of order (lag) 1 month and a moving average of order 1 ($R^2 = 0.22$).

Rates of antibiotic use

Monthly rates of antimicrobial use are detailed in Table 1 and Figure 3. The average antimicrobial use over the study period was 33 DDD/100 patients-days and did not change over time ($P = 0.29$). Penicillins (WHO class, J01C) were the most widely used antibiotic class (30%; pooled rate, 9.84 DDD/100 patient-days), followed by cephalosporins and carbapenems (J01D: 25%; pooled rate, 8.25 DDD/100 patient-days), fluoroquinolones (J01M), macrolides (J01F), trimethoprim/sulfamethoxazole (J01E) and glycopeptides (J01X) (Table 1).

Intervention model of the use of ABHRs

Consumption of ABHRs increased over the study period, from an average of 1.303 L per 100 patient-days in 2001 to 2.016 L per 100 patient-days in 2006. We identified an ARIMA model ($R^2 = 0.95$) with two significant autoregressive terms of order (lag) 1 and 3 months. The intervention model detailed in Table 2 showed statistically significant effects at a contemporaneous time of the *VigiGerme*® campaign and the '*Clean care is safer care*' campaign.

Table 1. Monthly time series of antimicrobial use and temporal relation with MRSA and *C. difficile*, February 2000 to September 2006

WHO classification	Antimicrobial use	Average monthly use (min–max)	Percentage of total use	Trend	*P*	Temporal relation with MRSA	Temporal relation with *C. difficile*
J01C	amoxicillin/clavulanate	6.39 (4.50–9.26)	19	−0.0242	0.001	no	no
	amoxicillin	3.22 (1.89–4.28)	10	0.0059	0.026	no	no
	piperacillin/tazobactam	0.23 (0.01–1.30)	1	0.0098	<0.001	yes	no
J01D	cefuroxime	2.46 (1.78–3.39)	7	−0.0002	0.926	no	yes
	third-generation cephalosporins	2.87 (1.79–4.18)	9	0.0132	<0.001	yes	yes
	cefepime	1.82 (0–2.77)	6	−0.0372	0.015	yes	yes
	carbapenems	1.10 (0.61–1.65)	3	0.9259	0.336	no	no
J01M	fluoroquinolones	5.41 (4.06–7.02)	16	−0.0023	0.478	yes	no
J01F	macrolides	2.27 (1.00–3.72)	7	0.0040	0.033	yes	no
	clindamycin	0.58 (0.06–1.27)	2	0.0052	<0.001	no	no
J01E	trimethoprim/sulfamethoxazole	1.01 (0.47–1.50)	3	0.0033	0.004	no	no
J01X	glycopeptides	0.84 (0.33–1.25)	3	−0.0019	0.003	no	no

MRSA, methicillin-resistant *S. aureus*; WHO, World Health Organization.

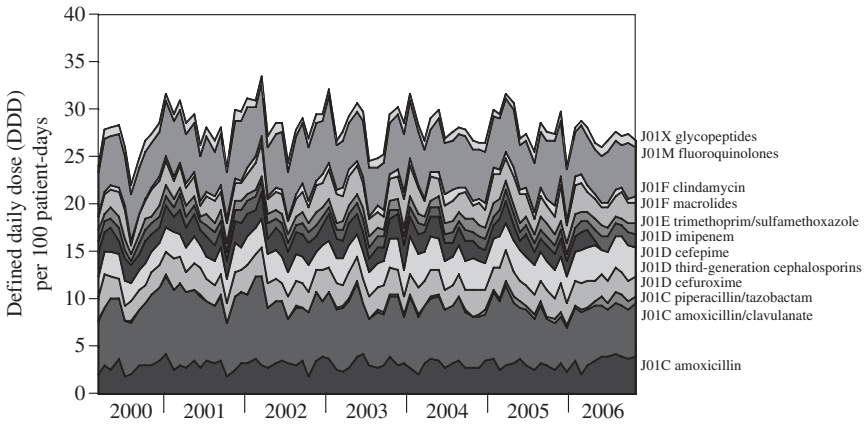

Figure 3. Monthly rates of antimicrobial use in DDDs per 100 patient-days. University of Geneva Hospitals, February 2000 to September 2006. The abbreviations shown (e.g. J01X) correspond to the WHO nomenclature of the different classes of antimicrobial agents.

Final models

Methicillin-resistant S. aureus. We built a first transfer function model by combining the analysis on hand rub consumption with monthly rates of antibiotic use, and then determined their effect on MRSA incidence. The generated model showed an autoregressive term of order 1 and a moving average of order 1 with an R^2 of 0.57, which means that the overall model explains 57% of the MRSA variance (Figure 4).

The estimated parameters obtained by unconditional least square method are shown in Table 3. In this model, there are six statistically significant explanatory variables, fluoroquinolone use (lag 1 month), macrolide use (lag 1 and 4 months), third-generation cephalosporin use (lag 4 and 5 months), cefepime use (lag 3 months), piperacillin/tazobactam use (lag 3 months) and the '*Clean care is safer care*' campaign at a contemporaneous time. Neither the *VigiGerme*® campaign, nor the bed occupancy rate or the use of other agents (amoxicillin, amoxicillin/clavulanic acid, cefuroxime, carbapenem, clindamycin, trimethoprim/sulfamethoxazole and glycopeptides) was statistically significant in this model. All of the included parameter estimates for antibiotic use were positive, meaning that an increase of 1 U would increase MRSA incidence. Thus, an increase of 1 DDD/100 patient-days of antibiotic use will be associated with an increase in the number of MRSA isolates from the current level, i.e. 0.01 for fluoroquinolones, 0.03 for macrolides, 0.03 for third-generation cephalosporins, 0.01 for cefepime and 0.04 for piperacillin/tazobactam. Conversely, the second hand hygiene campaign reduced the MRSA incidence; 1 L of hand rub per 100 patient-days decreased the MRSA by 0.03 isolates per 100 patient-days.

Clostridium difficile. We built another transfer function model for *C. difficile* incidence. This model shows an autoregressive term of order 1, where R^2 was low (0.17), meaning that the overall model explains only 17% of the *C. difficile* variance. In this model, there was only one statistically significant

Table 2. Intervention model analysing the effect of two promotion campaigns on ABHR use; University Hospitals of Geneva, February 2000 to September 2006

Variable	Parameter (SE)[a]	*t* statistic	*P* value
Constant	1.362 (0.044)	31.22	<0.0001
VigiGerme® campaign (spring 2003)	0.390 (0.049)	8.03	<0.0001
'*Clean care is safer care*' campaign (autumn 2005)	0.189 (0.057)	3.34	0.0013
ICU delivery 1[b]	0.921 (0.071)	12.90	<0.0001
ICU delivery 2[b]	0.903 (0.076)	11.91	<0.0001
AR (order 1)[c]	0.236 (0.111)	2.13	0.0365
AR (order 3)[c]	0.447 (0.107)	4.17	0.0001

[a]Size and direction of the effect.
[b]'ICU deliveries' 1 and 2 represent the artificial increases of ABHR use due to massive over-ordering and exceptional delivery of large quantities of alcohol-based hand gels to the adult intensive care units (ICUs) in 2004 and 2006.
[c]The autoregressive (AR) term represents the past value of ABHR use at months 1 and 3.

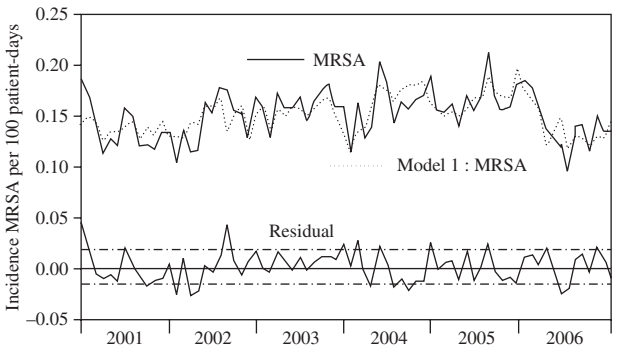

Figure 4. Transfer function model with analysis of MRSA incidence. University of Geneva Hospitals, February 2000 to September 2006.

explanatory variable, i.e. the use of broad-spectrum cephalosporins (lag 1 month; parameter, 0.0045; SE, 0.002; $P = 0.026$). In contrast, neither the use of ABHRs nor other antibiotic classes showed statistically significant correlations with *C. difficile* incidence.

Discussion

The main result of this study is that we found not only a temporal relation between MRSA incidence and the consumption of several classes of antibiotics, but also demonstrated the efficiency of a campaign focusing on hand hygiene promotion through proper use of ABHRs. The final model allows quantification of the effect of antibiotic use on MRSA and estimated the delay between variations in antimicrobial use and resistance. The transfer function model on MRSA explains 57% of the variance which is relatively high for this type of ecological analysis. Yet, 43% of the variation remain unexplained and could be

Table 3. Multivariate transfer function model for incidence of MRSA; University of Geneva Hospitals, February 2000 to September 2006

Variable	Lag[a] (months)	Parameter[b] (SE)	*t* statistic	*P*
Constant		−0.079 (0.030)	−2.62	0.011
Fluoroquinolones	1	0.010 (0.004)	2.71	0.009
Macrolides	1	0.014 (0.004)	3.61	<0.001
Macrolides	4	0.012 (0.004)	3.19	0.002
Third-generation cephalosporins	4	0.014 (0.006)	2.15	0.035
Third-generation cephalosporins	5	0.015 (0.007)	2.21	0.031
Cefepime	3	0.014 (0.006)	2.56	0.013
Piperacillin/ tazobactam	3	0.041 (0.014)	2.97	0.004
'*Clean care is safer care*' campaign's effect	0	−0.032 (0.005)	−5.81	<0.001
Autoregressive term[c]	1	0.546 (0.168)	3.24	0.002
Moving average term[d]	1	−0.732 (0.164)	−4.46	<0.001

The transfer function model can also be presented as the following equation: $\mathrm{MRSA}_{(t)} = -0.08 + 0.54\ \mathrm{MRSA}_{(t-1)} + 0.01$ fluoroquinolones $+ 0.03$ macrolides $+ 0.03$ third-generation cephalosporins $+ 0.014$ cefepime $+ 0.04$ piperacillin/tazobactam $- 0.03$ second hand hygiene campaign.
[a]Delay necessary to observe the effect.
[b]Size and direction of the effect.
[c]The autoregressive term represents the past value of the resistance.
[d]The moving average term represents disturbances or abrupt changes of resistance.

linked to patient factors, infection control practices and environmental characteristics. In contrast, our results did not find any correlation between the increasing use of ABHRs and the incidence of *C. difficile* at our institution. The model on *C. difficile* explains only 17% of the variation, thus rejecting a detrimental effect of ABHR use.

Different types of studies have been used to quantify the association between antibiotic use and the incidence of MRSA or *C. difficile* in hospitalized patients. These studies included outbreak reports, prevalence surveys, controlled trials, meta-analyses and prospective or retrospective cohort studies based on analyses of individual patient-level data or aggregated data.[7,26–34] The different methodological approaches are not mutually transposable, and the lack of uniformity makes the comparison of different studies difficult.[2] Our findings confirm, however, the important effect of different antibiotic classes on the selection of MRSA (e.g. cephalosporins, fluoroquinolones), reported in previously published time-series analyses.[7,25,35]

We confirmed the previous reports about the impact of improved hand hygiene practices on MRSA.[4,6] Our models show an immediate effect of increasing ABHR use after the second campaign; in contrast, we observed lag effects up to 5 months of antibiotic usage on MRSA incidence that are not plausible from an epidemiological perspective, particularly in a hospital in which the mean stay is ~8 days. However, it has been shown that environmental contamination may be sustained. An

interventional cohort study reported a 6 month delay in the decline of *C. difficile*-associated diarrhoea after virtual withdrawal of all cephalosporins which may reflect a slowly diminishing environmental reservoir.[36] To a lesser degree, this phenomenon may also apply for MRSA. As shown by two recent studies, withdrawal of fluoroquinolones or reduction of macrolide use may cause a measurable ecological effect on MRSA incidence only after several months.[7,31]

Modelling drug use versus susceptibility relations is a useful tool for complementing traditional surveillance and epidemiological studies. In our institution, it helped policy-making by estimating which drugs have an important impact on MRSA acquisition. Thus, antibiotic stewardship strategies could be tailored to the results of this multivariate time-series analysis, which allows various explanatory variables to be examined in parallel. Moreover, this analysis allowed external benchmarking. In our hospital, compared with other institutions in high-income countries, the volume of antibiotic use is below average (despite the absence of an institutional antibiotic policy) and the consumption of ABHRs is high.[6,12,37,38]

Our study has several limitations. First, group-level analyses of aggregate data may be distorted by ecological bias.[39] Modelling of individual patient-level data or multilevel data should complement time-series analyses to exclude spurious findings.[30] The availability of electronic prescribing records may allow us to perform combined analyses at both individual and group levels.[40] Second, DDD represents a technical unit that may not represent the true prescription data and may be wrong in children, patients with renal impairment and other co-morbidities.[38] Nevertheless, this method is still the most widely applied because of its potential for internal and external benchmarking. Third, we did not exclude the clinical MRSA isolates retrieved within 48 h after admission. This decision was based on the knowledge that community MRSA is still very rare in Geneva and that the vast majority of MRSA-infected patients detected upon admission had a previous hospital stay at HUG and were infected by a single MRSA clone (ST 228-MRSA-I) endemic at HUG.[28,41,42] Finally, the *VigiGerme*® campaign did not have a significant effect on MRSA incidence in the multivariate analysis. This finding could be explained either by the neutralizing effect of temporarily increased use of fluoroquinolones or by the fact that this campaign was not focused on hand hygiene promotion and targeted many other aspects of standard and contact precautions. In contrast, the second campaign '*Clean care is safer care*' promoted a user-centred concept of hand hygiene.[43]

In conclusion, we found an aggregate-level relationship between monthly MRSA incidence and the consumption of ABHRs and different antibiotic classes, while no association with increased hand rub use was detected for *C. difficile*.

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Transparency declarations

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